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# Asymmetric amplification in the catalytic enantioselective 1,2-addition of Grignard reagents to enones†

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Francesca Caprioli, Ashoka V. R. Madduri, Adriaan J. Minnaard\* and Syuzanna R. Harutyunyan\*

**Large asymmetric amplification originating from solubility differences between the enantiopure and the racemic catalyst is observed in the addition of Grignard reagents to enones. This behaviour is not reaction or catalyst specific and is observed for metal complexes of a variety of chiral diphosphine ligands, extensively used in asymmetric catalysis.**

Catalytic enantioselective addition of organometallic reagents to aldehydes and ketones is in principle one of the most straightforward methods for the synthesis of chiral enantiopure secondary and tertiary alcohols.<sup>1</sup> The metal-catalyzed enantioselective version of this key transformation has been studied extensively using dialkylzinc, organoboron, organoaluminium, silicon and, very recently, Grignard reagents.<sup>2,3a-c</sup> In a number of these reactions it was shown that the relationship between  $ee_{\text{prod}}$  and  $ee_{\text{cat}}$  is non-linear, and therefore asymmetric amplification or depletion was observed.<sup>4</sup> Asymmetric amplification is a beneficial situation which allows the use of a non-enantiopure chiral catalyst to achieve maximum enantioselectivity. This phenomenon is usually specific for a given combination of chiral catalyst and reaction.<sup>4</sup>

Here we report that the asymmetric 1,2-addition of Grignard reagents to enones, catalysed by a chiral copper complex of ferrocenyl diphosphine ligand **L1**, displays an exceptionally large asymmetric amplification and affords high levels of enantioselectivities using a nearly racemic catalyst. We found that the asymmetric amplification observed is not specific for this particular reaction but is in fact due to large differences in the solubility of the racemic and the enantiopure copper-complex. Remarkably, similar behaviour is observed for a number of metal complexes of diphosphine ligands widely used in asymmetric catalysis (Fig. 1) which makes this a widely applicable phenomenon.

Recently we have reported that a Cu-complex of **L1**, commonly used to catalyse 1,4-addition reactions of Grignard reagents to  $\alpha,\beta$ -unsaturated carbonyl compounds and therefore to prevent 1,2-addition reactions, is in fact an excellent catalyst for the formation

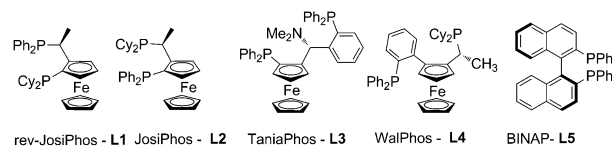
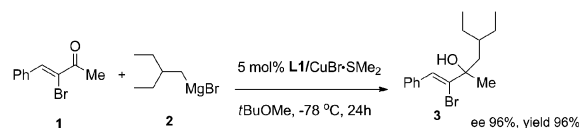


Fig. 1 Chiral diphosphine ligands used in this study.

of tertiary alcohols with high enantioselectivities.<sup>3a-c</sup> This study also comprised an investigation on the non-linear behaviour of the enantioselectivity using the 1,2-addition of Grignard reagent **2** to enone **1**. Using standard reaction conditions, product **3** was obtained with excellent yield and enantioselectivity (Scheme 1).

To study the asymmetric amplification phenomenon, scalemic Cu-complexes of **L1** with  $ee$ 's of 0%, 20%, 50% and 80% were prepared *in situ*. While preparing these solutions a significant amount of precipitate formed, prior to addition of the reactants. Subsequently, we studied the asymmetric amplification in two different ways. In the first run, the separated supernatant was used to catalyse the 1,2-addition. In the second run, the entire supernatant + precipitate of the complex was used. A large asymmetric amplification was observed in both runs (Table 1).



Scheme 1 Catalytic enantioselective 1,2-addition of a Grignard reagent to enone **1**.

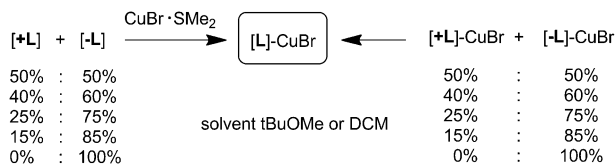
Table 1 Asymmetric amplification in the 1,2-addition of a Grignard reagent to enone **1**, catalysed by scalemic **L1**-Cu complexes

$ee$ , % Cu- <b>L1</b> , (loading, %)	$ee_{\text{s-p}}$ , <b>3</b> , % (conv. %)	$ee_{\text{s}}$ , <b>3</b> , % (conv. %)
20 (25)	80 (75)	94 (92)
40 (12)	90 (82)	94 (95)
60 (8)	90 (93)	92 (92)
80 (6)	90 (90)	94 (93)

$ee_{\text{s-p}}$  – reactions catalysed by a supernatant–precipitate mixture;  
 $ee_{\text{s}}$  – reactions catalysed by supernatant.

Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands. E-mail: s.harutyunyan@rug.nl, a.j.minnaard@rug.nl; Fax: +31-50-363-4296; Tel: +31-50-363-3539

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**Scheme 2** Preparation of scalemic copper complexes of **L1**–**L5**.<sup>5b</sup>

The enantioselectivity and conversion of the reactions catalyzed by the supernatants of the scalemic complexes were similar to the results obtained with the enantiopure catalyst (Table 1). Slightly lower ee's were obtained and longer reaction times were required (48 h) when the supernatant + precipitate mixtures were used to catalyse the reaction. This difference can be attributed to the presence of significant amounts of the precipitate (in particular for the Cu-complex with 20% ee) complicating efficient stirring.

To gain more insight into this phenomenon, the copper-complexes were prepared in *t*BuOMe (0.015 M) in two ways: (1) by mixing the enantioenriched chiral ligand **L1** with the corresponding amount of copper salt, for 30 min; (2) by mixing both enantiomers of *a priori* prepared enantiopure Cu-complex at room temperature, for 30 min (Scheme 2).<sup>5a</sup>

During the preparation of the Cu-complexes of **L1**, via either of these two methods, significant amounts of precipitate formed within 20–30 min of stirring while in the first 5 min everything was soluble. An exception was the solution of the Cu-complex of enantiopure **L1**, which even after prolonged stirring remained clear. The similar results obtained using both methods provide evidence that the whole process is under thermodynamic control. All samples were centrifuged and the precipitates separated from the supernatant. CD spectra (Fig. 2a) as well as optical rotations (Table 2, entry 1) were obtained for all the supernatants in *t*BuOMe. The ee of the solutions was >90% in all cases.<sup>6</sup>

Interestingly, the precipitate formed from the copper complex of **L1** was not soluble in most organic solvents. Nevertheless, based on the measured weight of the complexes from the solutions and precipitates and the fact that the ee of all the

**Table 2** Optical rotation values  $[\alpha]_D^{20}$  obtained from *t*BuOMe supernatant solutions of scalemic Cu- and Pd-complexes<sup>a,b,c</sup>

Entry	M-L	ee 20%	ee 50%	ee 70%	ee 100%
1	Cu- <b>L1</b>	–6 (–158)	–7	–7	–8 (–163)
2	Cu- <b>L2</b>	–185 (+363)	–191	–192	–198 (+376)
3	Cu- <b>L3</b>	+124 (+246)	+127	+122	+155 (+267)
4	Cu- <b>L5</b>	–75	–154	–189	–195
5	Pd- <b>L2</b>	–115	–122	–129	–211
6	Pd- <b>L3</b>	–117	–125	–144	–148

<sup>a</sup> Variations in  $[\alpha]_D^{20}$  values of enantioenriched samples are attributed to the presence of particles scattering the light. <sup>b</sup> Values enclosed by brackets correspond to ligands after treatment of the complexes with ethylenediamine (see ESI). <sup>c</sup>  $[\alpha]_D^{20}$  values of all the precipitates were negligible (see ESI).

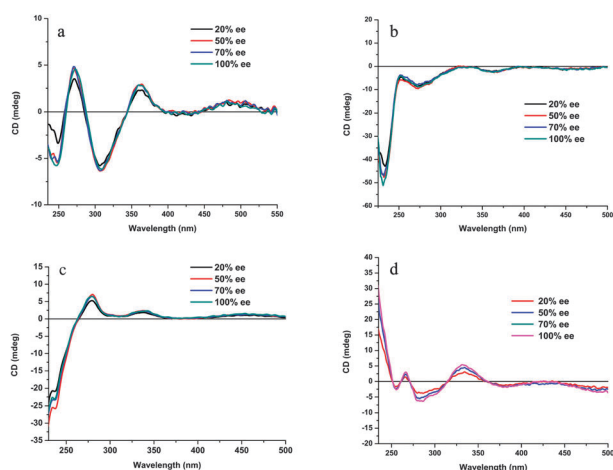
solutions exceeds 90%, it is certain that the precipitate in all the samples is approximately racemic (ee < 10%).

Next, we investigated whether it is possible to access the enantiopure free ligand **L1** from the corresponding scalemic copper complexes. For this purpose, a 20% ee solution of the Cu-complex of **L1**, in *t*BuOMe, was prepared and stirred for 12 h, followed by centrifugation and separation of the precipitate and supernatant. Both supernatant and precipitate were treated with ethylenediamine (en), in CH<sub>2</sub>Cl<sub>2</sub>, at 0 °C. After 1 h, the formation of the free ligand and CuBr(en) was complete. Upon purification using column chromatography, the enantiopure and racemic ligands of the corresponding complexes were obtained. The specific optical rotation of **L1** obtained from the supernatant is presented in Table 2 (entry 1, value enclosed by brackets).<sup>7</sup>

Metal complexes of chiral diphosphine ligands are extensively used as chiral catalysts in asymmetric synthesis.<sup>1,8</sup> Therefore we decided to investigate the generality of this phenomenon among metal complexes of various structurally different ferrocenyl diphosphine ligands commonly used in asymmetric catalysis (Fig. 1). Cu-complexes of enantioenriched **L2** were prepared in *t*BuOMe (0.015 M) as described for **L1**. Also in this case, a racemic precipitate was formed in *t*BuOMe, together with a virtually enantiopure solution (Fig. 2b, and Table 2, entry 2). The only difference with the previous example was that the precipitate was soluble in CH<sub>2</sub>Cl<sub>2</sub>. Similar results were obtained when copper complexes of **L2** with ee values of 20%, 50%, 70% and 100% were prepared in CH<sub>2</sub>Cl<sub>2</sub> (no precipitate formed) followed by solvent removal and addition of *t*BuOMe to the solid residues of the scalemic complexes. Samples were analysed after 24 h of stirring.

The higher solubility of the *t*BuOMe precipitate in CH<sub>2</sub>Cl<sub>2</sub> enabled us to demonstrate its racemic composition by using CD and optical rotation in CH<sub>2</sub>Cl<sub>2</sub>.<sup>5a</sup> The enantiopurity of the precipitate and supernatant was further ascertained by accessing the corresponding free ligand using ethylenediamine treatment (Table 2, entry 2, values enclosed by brackets).<sup>7</sup> Next, we determined the solubility of the complexes of enantiopure and racemic **L2** in *t*BuOMe to be 70 mg ml<sup>–1</sup> (0.12 M) and less than 0.1 mg ml<sup>–1</sup>, respectively. This difference in solubility is the primary factor for the observed enantioenrichment of the solutions of the scalemic complexes.

In the case of the structurally quite different ligand **L3**, which forms a seven-membered instead of a five-membered metallacycle upon complexation with the Cu ion, we also found the racemic complex to have a lower solubility than the enantiopure complex (2.2 mg ml<sup>–1</sup> and 5.3 mg ml<sup>–1</sup>, respectively). Thus, precipitation



**Fig. 2** CD spectra of the solutions (supernatants) of scalemic copper and palladium complexes (with 20%, 50%, 70% and 100% ee). The configuration of the major enantiomer is indicated: (a) CuBr-(*R,S*)-**L1** in CH<sub>2</sub>Cl<sub>2</sub>; (b) CuBr-(*R,S*)-**L2** in *t*BuOMe; (c) CuBr-(*R,R*)-**L3** in *t*BuOMe; (d) PdCl<sub>2</sub>-(*R,S*)-**L2** in *t*BuOMe.

from the scalemic mixture leads to a supernatant solution containing a complex with an ee > 90%, further supported by ethylenediamine treatment (Fig. 2c, and Table 2, entry 3).<sup>7</sup> For the Cu-complex of ferrocenyl ligand **L4**, we found the effect to be the opposite: the precipitate had a much higher enantiopurity than the corresponding supernatant which contained the nearly racemic complex.<sup>5a</sup>

We were curious whether this phenomenon is somewhat specific to ferrocenyl ligands and therefore performed similar experiments with binaphthyl phosphine ligand **L5** (BINAP). For this complex we had to use a solvent mixture (*t*BuOMe–CH<sub>2</sub>Cl<sub>2</sub>) due to the poor solubility of the enantiopure complex in pure *t*BuOMe. In this case, while the difference in solubility between racemic and enantiopure samples was less extreme (10 mg ml<sup>−1</sup> and 40 mg ml<sup>−1</sup>, respectively), significant enantioenrichment was still observed (Table 2, entry 4).<sup>5a</sup>

The next question to assess was whether metal complexation is required for this phenomenon to occur, and whether it is unique to copper. Scalemic JosiPhos-**L1** (with 0%, 20%, 50% and 70% ee) was stirred for 24 h in *t*BuOMe as well as in CH<sub>2</sub>Cl<sub>2</sub>, both at room temperature and at 0 °C. No precipitate was formed, clearly indicating that it is the metal complexation that changes the solid-solution phase behaviour of these chiral diphosphine ligands in the provided solvents.

We also prepared scalemic mixtures of the Pd complexes with **L2** and **L3** in a mixture of *t*BuOMe–CH<sub>2</sub>Cl<sub>2</sub>, and found that the phenomenon also persists in these cases (Table 2, entries 5 and 6). Similar to the results obtained for the Cu-complex of BINAP, the difference in solubility between the racemic (2.5 mg ml<sup>−1</sup>) and enantiopure (12 mg ml<sup>−1</sup>) Pd complex of **L2** was less extreme, resulting in a lower ee value at the eutectic (Fig. 2d, and Table 2, entry 5).<sup>5a</sup> For the Pd complex of **L3**, the solubilities of the racemic and enantiopure samples were 0.3 mg ml<sup>−1</sup> and 14.4 mg ml<sup>−1</sup> respectively, and the ee's of all the supernatants were >80% (Table 2, entry 6).<sup>5a</sup>

It is a general trend that crystals of racemates are more stable than those of their single enantiomers but extreme differences in their stability, allowing efficient separation, are rare.<sup>9</sup> The introduction of intermolecular interactions, e.g. H-bonding or ionic interactions, can amplify the solubility difference which is probably the reason behind a number of asymmetric amplifications, based on a dual phase behaviour, reported for reactions utilising chiral derivatives of amino acids, diaminocyclohexane, bisoxazoline and phosphoric acid as catalysts.<sup>10</sup> Although crystalline solids, the chiral ligands explored in this study lack the possibility of intermolecular hydrogen bonding or ionic interactions. It is most likely that the formation of metal complexes acts as a surrogate for such interactions leading to the formation of homo- and hetero-chiral species with different solubilities.

To understand the role of the metal in inducing this large difference in solubility, we studied the nature of the enantiopure and racemic copper complexes of **L1–L3** formed using ESI-MS spectrometry performed in *t*BuOMe and CH<sub>2</sub>Cl<sub>2</sub>. This study showed that in solution both dimeric and monomeric structures are present. <sup>1</sup>H- and <sup>31</sup>P-NMR spectroscopy of the

copper complexes of **L1–L3** (in CD<sub>2</sub>Cl<sub>2</sub>) showed identical spectra for both the racemate and the single enantiomers.<sup>3d,5</sup> Further studies including structural characterization of chiral metal complexes in the solid state will be required to elucidate the mechanistic aspects of this phenomenon.

In summary, we have found that complexation of a transition metal with chiral diphosphine ligands induces an extreme difference in the solubility between the racemates and the single enantiomers, an effect which is absent in the case of the free ligands. This phenomenon is responsible for a large asymmetric amplification observed in the 1,2-addition of Grignard reagents to enones and furthermore allows the efficient separation of racemic and enantiopure complexes from a scalemic mixture by simple filtration.

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- (a) For details see ESI†; (b) For simplicity we depicted only monomeric species, however ESI-MS spectrometry revealed both monomeric [L]-CuBr and dimeric ([L]-CuBr)<sub>2</sub> species in solution<sup>5a</sup>.
- The enantiopurity of the supernatants was estimated by comparison with values of the enantiopure complexes using CD spectroscopy and polarimetry. The error for the specific optical rotation values is typically 5% (see ESI†).
- Measuring [α]<sub>D</sub><sup>20</sup> of the free ligand provided a more accurate ee determination due to the higher net value of the rotation. Furthermore, particles were present in solution scattering the light and interfering with the results. For details see ESI†.
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